Facts About Dietary Supplements

Clinical Nutrition Service, Warren Grant Magnuson Clinical Center • Office of Dietary Supplements • National Institutes of Health

Folate

As a consumer, you need information you can trust to help you make thoughtful decisions about eating a healthful diet and using vitamin and mineral supplements. Registered dietitians at the Warren Grant Magnuson Clinical Center, the clinical research hospital at the National Institutes of Health (NIH) in Bethesda, MD, developed this series of Fact Sheets in conjunction with the Office of Dietary Supplements in the Office of the Director of NIH to provide responsible information about the role of vitamins and minerals in health and disease and to help guide your decisions on the use of vitamin and mineral supplements. Each fact sheet in this series received extensive scientific review by recognized experts from the academic and research communities.

The information is not intended to be a substitute for professional medical advice. It is important that you seek the advice of a physician about any medical condition or symptom. It is also important to seek the advice of a physician, registered dietitian, pharmacist, or other qualified health care professional about the appropriateness of taking dietary supplements and their potential interactions with medications.

Folate: What is it?

Folate and folic acid are forms of a water-soluble B vitamin. Folate occurs naturally in food. Folic acid is the synthetic form of this vitamin that is found in supplements and fortified foods (1).

Folate gets its name from the Latin word “folium” for leaf. A key observation of researcher Lucy Wills nearly 70 years ago led to the identification of folate as the nutrient needed to prevent the anemia of pregnancy. Dr. Wills demonstrated that the anemia could be corrected by a yeast extract. Folate was identified as the corrective substance in yeast extract in the late 1930s and was extracted from spinach leaves in 1941.

Folate is necessary for the production and maintenance of new cells (2). This is especially important during periods of rapid cell division and growth such as infancy and pregnancy. Folate is needed to make DNA and RNA, the building blocks of cells. It also helps prevent changes to DNA that may lead to cancer (3). Both adults and children need folate to make normal red blood cells and prevent anemia (4).

What foods provide folate?

Leafy greens such as spinach and turnip greens, dry beans and peas, fortified cereals and grain products, and some fruits and vegetables are rich food sources of folate. Some breakfast cereals (ready-to-eat and others) are fortified with 25% or 100 percent of the Daily Value (DV) for folic acid. The table of selected food sources of folate and folic acid suggests dietary sources of this vitamin (5).

In 1996, the Food and Drug Administration (FDA) published regulations requiring the addition of folic acid to enriched breads, cereals, flours, corn meals, pastas, rice, and other grain products (6-8). This ruling took effect January 1, 1998, and was specifically targeted to reduce the risk of neural tube birth defects in newborns (9). Since the folic acid fortification program took effect, fortified foods have become a major source of folic acid in the American diet.

Synthetic folic acid that is added to fortified foods and dietary supplements has a simpler chemical structure than the natural form of folate, and is absorbed more easily by the body. After digestion and absorption however, the two forms are identical and function in exactly the same manner.

What is the Recommended Dietary Allowance for folate for adults?

The Recommended Dietary Allowance (RDA) is the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97 to 98 percent) healthy individuals in each life-stage and gender group (10). The 1998 RDAs for folate are expressed in a term called the Dietary Folate Equivalent. The Dietary Folate Equivalent (DFE) was developed to help account for the differences in absorption of naturally occurring dietary folate and the more bioavailable synthetic folic acid (11). The 1998 RDAs for folate expressed in micrograms (mcg) of DFE for adults are (10):

Life Stage	Men	Women	Pregnancy	Lactation
Ages 19+	400 mcg	400 mcg		
All ages			600 mcg	500 mcg

1 mcg of food folate = 0.6 mcg folic acid from supplements and fortified foods

The National Health and Nutrition Examination Survey (NHANES III 1988-91) and the Continuing Survey of Food Intakes by Individuals (1994-96 CSFII) indicated that most adults did not consume adequate folate (10, 12, 13). However, the folic acid fortification program has increased folic acid content of commonly eaten foods such as cereals and grains, and as a result diets of most adults now provide recommended amounts of folate equivalents (14).

When can folate deficiency occur?

A deficiency of folate can occur when your need for folate is increased, when dietary intake of folate is inadequate, and when your body excretes (or loses) more folate than usual.

Medications that interfere with your body's ability to use folate may also increase the need for this vitamin (1, 6, 15 -19).

Some situations that increase the need for folate include:

- pregnancy and lactation (breastfeeding)
- alcohol abuse
- malabsorption
- kidney dialysis
- liver disease
- certain anemias.

Medications can interfere with folate utilization, including:

- anticonvulsant medications (such as dilantin, phenytoin and primidone)
- Metformin (sometimes prescribed to control blood sugar in type 2 diabetes)

  Sulfasalazine (used to control inflammation associated with Crohn's disease and ulcerative colitis)
- Triamterene (a diuretic)
- Methotrexate.

Signs of folate deficiency

Signs of folate deficiency are often subtle.Diarrhea, loss of appetite, and weight loss can occur. Additional signs are weakness, sore tongue, headaches, heart palpitations, irritability, and behavioral disorders (1, 20). Women with folate deficiency who become pregnant are more likely to give birth to low birth weight and premature infants, and infants with neural tube defects. In adults, anemia is a sign of advanced folate deficiency. In infants and children, folate deficiency can slow growth rate. Some of these symptoms can also result from a variety of medical conditions other than folate deficiency. It may be important to have a physician evaluate these symptoms so that appropriate medical care can be given.

Who may need extra folic acid to prevent a deficiency?

Women of childbearing age, people who abuse alcohol, anyone taking anti-convulsants or other medications that interfere with the action of folate, individuals diagnosed with anemia from folate deficiency, and individuals with malabsorption, liver disease, or who are receiving kidney dialysis treatment may benefit from a folic acid supplement.

Folic acid is very important for all women who may become pregnant. Adequate folate intake during the periconceptual period, the time just before and just after a woman becomes pregnant, protects against a number of congenital malformations including neural tube defects (21). Neural tube defects result in malformations of the spine (spina bifida), skull, and brain (anencephaly) (10). The risk of neural tube defects is significantly reduced when supplemental folic acid is consumed in addition to a healthful diet prior to and during the first month following conception (5, 22, 23). Women who could become pregnant are advised to eat foods fortified with folic acid or take supplements in addition to eating folate-rich foods to reduce the risk of some serious birth defects. Taking 400 micrograms of synthetic folic acid daily from fortified foods and/or supplements has been suggested (10). The Recommended Dietary Allowance (RDA) for folate equivalents for pregnant women is 600 micrograms (10).

Folate deficiency has been observed in alcoholics. A 1997 review of the nutritional status of chronic alcoholics found low folate status in more than 50 percent of those surveyed (24). Alcohol interferes with the absorption of folate and increases excretion of folate by the kidney. In addition, many alcohol abusers have poor quality diets that do not provide the recommended intake of folate (17). Increasing folate intake through diet, or folic acid intake through fortified foods or supplements, may be beneficial to the health of alcoholics.

Anti-convulsant medications such as dilantin increase the need for folate (25,26). Anyone taking anti-convulsants and other medications that interfere with the body's ability to use folate should consult with a medical doctor about the need to take a folic acid supplement (27-29).

Anemia is a condition that occurs when red blood cells cannot carry enough oxygen. It can result from a wide variety of medical problems, including folate deficiency. Folate deficiency can result in the formation of large red blood cells that do not contain adequate hemoglobin, the substance in red blood cells that carries oxygen to your body's cells (4). Your physician can determine whether an anemia is associated with folate deficiency and whether supplemental folic acid is indicated.

Several medical conditions increase the risk of folic acid deficiency. Liver disease and kidney dialysis increase excretion (loss) of folic acid. Malabsorption can prevent your body from using folate in food. Medical doctors treating individuals with these disorders will evaluate the need for a folic acid supplement (1).

Caution about folic acid supplements

Beware of the interaction between vitamin B_{12} and folic acid. Folic acid supplements can correct the anemia associated with vitamin B_{12} deficiency. Unfortunately, folic acid will not correct changes in the nervous system that result from vitamin B_{12} deficiency. Permanent nerve damage can occur if vitamin B_{12} deficiency is not treated. Intake of supplemental folic acid should not exceed 1,000 micrograms (mcg) per day to prevent folic acid from masking symptoms of vitamin B_{12} deficiency (10).

It is very important for older adults to be aware of the relationship between folic acid and vitamin B_{12} because they are at greater risk of having a vitamin B_{12} deficiency. If you are 50 years of age or older, ask your physician to check your B_{12} status before you take a supplement that contains folic acid.

What are some current issues and controversies about folate?

Folic Acid and Heart Disease

A deficiency of folate, vitamin B_{12}, or vitamin B_6 may increase your level of homocysteine, an amino acid normally found in your blood. There is evidence that an elevated homocysteine level is an independent risk factor for heart disease and stroke (30 - 41). The evidence suggests that high levels of homocysteine may damage coronary arteries or make it easier for blood clotting cells called platelets to clump together and form a clot (36). However, there is currently no evidence available to suggest that lowering homocysteine with vitamins will reduce your risk of heart disease. Clinical intervention trials are needed to determine whether supplementation with folic acid, vitamin B_{12} or vitamin B6 can lower your risk of developing coronary heart disease.

Folic Acid and Cancer

Some evidence associates low blood levels of folate with a greater risk of cancer (42). Folate is involved in the synthesis, repair, and functioning of DNA, our genetic map, and a deficiency of folate may result in damage to DNA that may lead to cancer (43). Several studies have associated diets low in folate with increased risk of breast, pancreatic, and colon cancer (44, 45). Findings from a study of over 121,000 nurses suggested that long-term folic acid supplementation (for 15 years) was associated with a decreased risk of colon cancer in women aged 55-69 years of age (44). However, associations between diet and disease do not indicate a direct cause. Researchers are continuing to investigate whether enhanced folate intake from foods or folic acid supplements may reduce the risk of cancer. Until results from such clinical trials are available, folic acid supplements should not be recommended to reduce the risk of cancer.

Folic Acid and Methotrexate for Cancer

Folate is important for cells and tissues that rapidly divide (2). Cancer cells divide rapidly, and drugs that interfere with folate metabolism are used to treat cancer. Methotrexate is a drug often used to treat cancer because it limits the activity of enzymes that need folate.

Unfortunatley, methotrexate can be toxic (46-48), producing side effects such as inflammation in the digestive tract that make it difficult to eat normally. Leucovorin is a form of folate that can help “rescue” or reverse the toxic effects of methotrexate (49). It is not known whether

folic acid supplements can help control the side effects of methotrexate without decreasing its effectiveness in chemotherapy (50-51). *It is important for anyone receiving methotrexate to follow a medical doctor's advice on the use of folic acid supplements.*

Folic Acid and Methotrexate for Non-Cancerous Diseases
Low dose methotrexate is used to treat a wide variety of non-cancerous diseases such as rheumatoid arthritis, lupus, psoriasis, asthma, sarcoidoisis, primary biliary cirrhosis, and inflammatory bowel disease (52). Low doses of methotrexate can deplete folate stores and cause side effects that are similar to folate deficiency. Both high folate diets and supplemental folic acid may help reduce the toxic side effects of low dose methotrexate without decreasing its effectiveness, (53, 54). Anyone taking low dose methotrexate for the health problems listed above should consult with a physician about the need for a folic acid supplement.

What is the health risk of too much folic acid?
The risk of toxicity from folic acid is low (55). The Institute of Medicine has established a tolerable upper intake level (UL) for folate of 1,000 mcg for adult men and women, and a UL of 800 mcg for pregnant and lactating (breast-feeding) women less than 18 years of age (10). Supplemental folic acid should not exceed the UL to prevent folic acid from masking symptoms of vitamin B_{12} deficiency (10, 29).

Selected food sources of folate and folic acid
As the 2000 Dietary Guidelines for Americans state, "Different foods contain different nutrients and other healthful substances. No single food can supply all the nutrients in the amounts you need" (56). The following table suggests dietary sources of folate. As the table indicates, green leafy vegetables, dry beans and peas, and many other types of vegetables and fruits are good sources of folate. In addition, fortified foods are a major source of folic acid. It is not unusual to find foods such as cereals fortified with 100 percent of the RDA for folate. The variety of fortified foods available has made it easier for women of childbearing age to consume the recommended 400 mcg of folic acid per day from fortified foods and/or supplements (6). The large numbers of fortified foods on the market, however, also raise concern that intake may exceed the UL. This is especially important for anyone at risk of vitamin B12 deficiency, which can be masked by too much folic acid. It is important for anyone who is considering taking a folic acid supplement to first consider whether their needs are being met by adequate sources of dietary folate and folic acid from fortified foods.

If you want more information about building a healthful diet, refer to the Dietary Guidelines for Americans and the Food Guide Pyramid.

Table of Selected Food Sources of Folate (5)

Food	*Micrograms Dietary Folate Equivalents*	*% DV**
Ready to eat cereal, fortified with 100% of the DV 3/4 c	400	100
Beef liver, cooked, braised, 3 oz	185	45
Cowpeas (blackeyes), immature, cooked, boiled 1/2 c	105	25
Breakfast cereals, fortified with 25% of the DV 3/4 c	100	25
Spinach, frozen, cooked, boiled1/2 c	100	25
Great Northern beans, boiled, 1/2 c	90	20
Asparagus, boiled, 4 spears	85	20
Wheat germ, toasted, 1/4 c	80	20
Orange juice, chilled, includes concentrate, 3/4 c	70	20
Turnip Greens, frozen, cooked, boiled, 1/2 c	65	15
Vegetarian baked beans, canned, 1 c	60	15
Spinach, raw, 1 c	60	15
Green peas, boiled, 1/2 c	50	15
Broccoli, chopped, frozen, cooked, 1/2 c	50	15
Egg noodles, cooked, enriched, 1/2 c	15	50
Rice, white, long-grain, parboiled, cooked, enriched, 1/2 c	45	10

Table of Selected Food Sources of Folate (5)

Food	*Micrograms Dietary Folate Equivalents*	*% DV**
Avocado, raw, all varieties, sliced 1/2 c sliced	45	10
Peanuts, all types, dry roasted, 1 oz	40	10
Lettuce, Romaine, shredded, 1/2 c	40	10
Tomato Juice, canned, 6 oz	35	10
Orange, all commercial varieties, fresh, 1 small	30	8
Bread, white, enriched, 1 slice	25	6
Egg, whole, raw, fresh, 1 large	25	6
Cantaloupe, raw, 1/4 medium	25	6
Papaya, raw, 1/2 c cubes	25	6
Banana, raw, 1 medium	20	6
Broccoli, raw, 1 spear (about 5 inches long)	20	6
Lettuce, Iceberg, shredded,1/2 c	15	4
Bread, whole wheat, 1 slice	15	4

***** DV = Daily Value. DVs are reference numbers based on the Recommended Dietary Allowance (RDA). They were developed to help consumers determine if a food contains a lot or a little of a specific nutrient. The DV for folic acid is 400 micrograms (mcg). The percent DV (%DV) listed on the nutrition facts panel of food labels tells adults what percentage of the DV is provided by one serving. Percent DVs are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs. Foods that provide lower percentages of the DV also contribute to a healthful diet.

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